Guidance for Use of Electronic Records in Clinical Trials

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Electronic Records in Clinical Trials

- Review provisions of draft guidance on Computerized Systems Used in Clinical Trials
- Present an overview of public comments received on the guidance
- Report on progress toward resolving comments and finalizing the guidance

Introduction

- Guidance versus Regulation
- Clinical trial records covered by regulation
- Quality expectations for records used in regulatory decision making

Guidance for Industry

Computerized Systems Used in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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Guidance

- Represents the Agency's current thinking
- Not binding on FDA or the public
- An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations or both.
- Guidance does not limit the authority of a Center and should not supplant discussions between Centers and sponsors.

Regulatory Requirements for Clinical Trial Records

- IND regulations 21 CFR 312
  - 312.62(b) Prepare and maintain adequate and accurate case histories
  - 312.68 Permit FDA to have access to, and copy and verify any records or reports required under 312.62(b)
- 21 CFR 11 applies if the above are electronic

Case Histories

- Record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control
- Includes the Case Report Form and supporting data

Case Histories

- **Supporting Data**
  - **found in original records or verified copies is source data**
  - **source data is found in source documents**

Source Documents

- Hospital records
- Office Charts
- Lab reports
- Memoranda
- Subject diaries
- Pharmacy dispensing records
- X-rays
- case report forms when data is entered directly
- magnetic media
- photographic negatives

Source Data

- Medical history information
- Medical examination results
- All lab results
- Demographic data
  - DOB -sex -weight
  - Age -race -height
- Concomitant Meds
- Patient ID number
- Study number
- Drug dispensing information
- Informed consent
- IRB approval
- Visit dates
- Intercurrent illness

Electronic Data Quality in the Clinical Environment

- **Reliability of data for decision-making, whether electronic or paper, is dependent upon meeting quality expectations**
- **Guidance attempts to articulate how elements of data quality might be satisfied for electronic data in the clinical environment**

Traditional Data Quality Expectations

- Elements of Data Quality
  - **Attributable**
  - **Legible**
  - **Contemporaneous**
  - **Original**
  - **Accurate**

Traditional Data Quality Expectations

- Implicit in regulations and guidance
  - **Drug and Device GMPs**
  - **GLPs**
  - **GCP Regulations and Guidance**

Draft Guidance General Principles

- When original observations are entered directly into a computer system the electronic record is the source data
  - **source data are contained in source documents**
  - **source document = original record = certified copy**

Draft Guidance General Principles

- Computerized system should ensure that all applicable regulatory requirements for record keeping and records retention in clinical trials are met with at least the same degree of confidence as is provided with paper systems

Draft Guidance General Principles

- Clinical investigators should retain copies of all records and underlying data sent to the sponsor/CRO including query resolution correspondence
  - **even though the sponsor has the record**
  - **copy or original**

Draft Guidance
General Principles

- Any correction to a record required to be maintained should not obscure the original entry
- Changes to data stored on electronic media will require an audit trail. For changes made at the research site, the clinical investigator's documentation should include who made changes, and when, how, why

Draft Guidance General Principles

- FDA may audit any and all records that might support submissions to the Agency, regardless of how they were created or maintained
  - Hardware and software used to generate and maintain electronic records and signatures are pertinent equipment subject to inspection

Draft Guidance
General Principles

- Data should be retrievable in such a fashion that all information regarding each individual subject in a study is attributable to that subject.

Draft Guidance General Principles

- Computerized systems should be designed so that all requirements outlined in a study protocol are satisfied
- Study protocols should state which computerized systems are to be used for generation, collection, maintenance, and transmission of data

Draft Guidance
General Principles

- Security measures should be in place to prevent unauthorized access to the data and the data collection device
  - **Physical**
  - **Logical**

Draft Guidance Standard Operating Procedures

SOPs should be available at the clinical site and should address:

- **System Setup/Installation**
- **Data Collection**
- **System Maintenance**
- **Data Backup and Recovery**
- **Security**
- **Change Control**

Draft Guidance Data Entry

- Electronic Signatures
  - **Data entry system should be designed so that individuals need to enter electronic signatures, e.g. combined password/usernames or biometric-based electronic signatures, before entering information for a given data entry session.**

Draft Guidance
Data Entry

- Each entry to an electronic record, including any change, should be made under the electronic signature of the individual making that entry
  - Printed name of individual making an entry should be visible on screen
  - Passwords should not be shared and should be changed at regular intervals

Draft Guidance Audit Trails

- Audit Trails per 21 CFR 11
  - **Secure, computer-generated, time-stamped**
  - **For entries and actions that create, modify, or delete electronic records.**
  - **Must not obscure previously recorded information**
  - **Documentation must be retained and available for Agency review and copying**

Draft Guidance System Design

- Features to Facilitate Quality Data
  - **Prompts, Flags, Help Features**
    - **consistent use of clinical terminology**
    - **out of range values**
  - **Annotation capabilities for patient diaries and case report forms**

Draft Guidance System Design

- Features to facilitate inspection and review of data
  - **Tags to indicate which data have been changed or deleted**
  - **Support for system**
    - **to ensure integrity of data over life of study**
    - **as necessary for record retrieval and review**

Draft Guidance Security

- Physical Security/External Safeguards
  - **To restrict access (data collection system and data) to authorized personnel**
  - **Personnel trained in system security measures**
  - **Documentation of authorized staff and access privileges**

Draft Guidance Security

- Physical Security/External Safeguards
  - **SOPs for system handling and storage to prevent unauthorized access**
  - **Lock-and-key storage of data and collection devices**

Draft Guidance Security

- Logical Security
  - **Access to database restricted through the system's software with its required log-on, security procedures, and audit trail**
  - **Data should not be altered, browsed, queried or reported via external software applications that do not enter through the protective system software**

Draft Guidance Security

- Logical Security
  - **Computer systems supplied exclusively for a clinical trial should remain so dedicated**
  - **For nondedicated systems, study software should be logically and physically isolated as needed to preclude unintended interaction with non-study software**

Draft Guidance
System Dependability

- Sponsor to ensure and document that the system conforms to established requirements for completeness, accuracy, reliability, and consistent performance for the intended purpose

Draft Guidance
System Dependability

- Documentation Available On-site
  - **Overall description of computerized operations and the relationship of hardware, software and physical environment**
  - **Validation of software if requested**
    - **sponsor responsibility**
    - **clinical investigator not generally responsible unless originated or modified software**

Draft Guidance
System Dependability

- Software Validation Documentation
  - **Written design specifications**
  - **Written test plan based on design specifications**
  - **Test results and evaluation to demonstrate predetermined criteria have been met**

Draft Guidance
System Dependability

- Off-the-Shelf Software
  - **Most validation is the responsibility of the author of the software**
  - **Sponsor should have**
    - **documentation of design level validation by the vendor**
    - **itself performed functional testing**

Draft Guidance
System Dependability

- Change Control
  - **Written procedures to ensure changes to system will not jeopardize the integrity of data**
  - **All changes should be documented**
  - **Changes that result in exceeding operational limits or design specification should precipitate revalidation**

Draft Guidance System Controls

- Software Version Control
  - **Measures to ensure versions used are those specified in systems documentation**
- Contingency Plans
  - **Written procedures for conducting the study by alternate means in the event of system failure**

Draft Guidance System Controls

- Backup and Recovery
  - **SOPs for backup and recovery procedures to prevent data loss**
    - **data should be backed up at regular intervals**
  - **Backup data stored at secure location**
    - **location specified in SOP**
    - **separate from original records**
    - **off-site storage recommended**

Draft Guidance System Controls

- Backup and Recovery
  - **Backup and recovery operations should be documented to permit assessment of the nature and scope of possible data loss resulting from system failure**

Draft Guidance
Training of Personnel

- Qualifications
  - **Personnel entering or processing data should have education, training and experience necessary to perform assigned functions**
  - **Monitors should have education, training, and experience in the use of the computerized system necessary to monitor the trial**

Draft Guidance
Training of Personnel

- Training
  - **Training should be provided to individuals in the specific operations they are to perform**
  - **Training should be conducted by qualified individuals on a continuing basis**
  - **Employee qualifications, training and experience should be documented**

Draft Guidance
Training of Personnel

- Training should cover at a minimum
  - **System setup/installation**
  - **Instruction in proper use of equipment**
  - **Data collection**
  - **System maintenance**
  - **Backup and recovery**
  - **Security measures**

Draft Guidance Records Inspection

- System should be able to generate records in human readable and electronic form
  - Suitable for inspection, review and copying by Agency
  - Persons should contact the Agency if there is any doubt about what file formats and media the Agency can read and copy

Draft Guidance Records Inspection

- Sponsor should be able to provide hardware and software as necessary for FDA personnel to inspect the electronic documents at the site where an FDA inspection is taking place

Comments on Draft Guidance

- Original comment period was extended to Nov. 3, 1997
- 23 respondents have offered a total of more than 500 comments to the docket
- FDA's CCT working group is presently reviewing comments and anticipates a finalized guidance by Spring 1998

Computerized Systems Used in Clinical Trials Working Group

CDER:

CarolAnne Currier
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Stan W. Woollen

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Pat Holobaugh
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Steven Musser
John Welsh

ORA:

James F. McCormack
Ted Sze

Comments on Draft Guidance

- **Who offered comments**
  - **5 trade associations representing manufacturers of pharmaceuticals, medical devices, blood products, and animal health care products**
  - **18 individual companies mostly pharmaceutical companies**

Most Notable Comments on Draft Guidance

- **Introduction**
  - **Clarify scope of systems covered**
- **Definitions**
  - **Ensure consistency of definitions with other FDA documents such as the glossary of computer terms**

Most Notable Comments on Draft Guidance

- **General Principles**
  - **"How" changes are made to data should be deleted (section H.)**
  - **Study protocol should not specify which computerized systems are used (section I)**
- **SOPs**
  - **Add additional SOPs**

Most Notable Comments on Draft Guidance

- **Data Entry**
  - **Name of individual entering data not necessary to appear on screen**
- **System Design**
  - **Need for annotation capability challenged**

Most Notable Comments on Draft Guidance

- **Security**
  - **Clarification requested on lock-and -key storage of data and collection devices**
- **System Dependability**
  - **Sponsors making validation documentation available for inspection at clinical trial site not practical**

Most Notable Comments on Draft Guidance

- **System Controls**
  - **Off-site storage of backup data and recommendation to specify storage location in SOP questioned**
- **Training of Personnel**
  - **Areas for training are specified in too much detail**

Draft Guidance Availability

- **Hard Copies:**

  Drug Information Branch (HFD-210)

  Division of Communications Management

  5600 Fishers Lane

  Rockville, Maryland 20857

Draft Guidance Availability

Electronic Via Internet

http://www.fda.gov/cder/guidance.htm

Overhead Copies

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  - **Look under "What's Happening" and select "Conferences, Meetings and Workshop Presentations by CDER Staff"**